Pseudo-Pelger-Huët anomaly induced by transplant medications

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Received: 3 March 2010 / Revised: 9 April 2010 / Accepted: 31 May 2010 / Published online: 16 June 2010
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A 67-year-old male with myelodysplastic syndrome (MDS) with complex cytogenetic abnormalities developed acute myeloid leukemia (AML) within a short period of darbe-poetin-alpha therapy. He received non-ablative chemotherapy followed by an allogeneic hematopoietic stem cell transplant (male donor). His post-transplant course was uneventful and within 1 month he achieved complete engraftment. Post-transplant medications included prednisone (80 mg per day as an initial dose, gradually tapered to 10 mg), mycophenolate mofetil (2,000 mg per day initially, reduced to 1,000 mg per day at 2-month status post-transplant), tacrolimus (1.5 mg per day, starting at 2-month status post-transplant), and other drugs. An automated complete blood count (CBC) 3 months post-transplant demonstrated a Hgb of 120 g/L (reference range 137–173 g/L), white blood count (WBC) of $2.8 \times 10^9/L$ (reference range $3.2\text{--}9.8 \times 10^9/L$) and platelets of $128 \times 10^9/L$ (reference range $150\text{--}450 \times 10^9/L$). A concurrent peripheral blood smear showed a few unilobed neutrophils with abnormally clumped chromatin consistent with pseudo-Pelger-Huët anomaly (PPHA). In the subsequent 9 months, the automated CBC demonstrated a mild pancytopenia, but the peripheral blood smear showed continuous increase of the PPHA cells, ultimately affecting 94% of neutrophils at approximately 1-year post-transplant. These PPHAs displayed a spectrum of nuclear contours, including round (a), oval (b), coffee bean-shaped (c), reniform (d), peanut-shaped (e), bilobed (f) and other forms (g). Some PPHAs also contained detached round nuclear

fragments in the cytoplasm, so-called Howell-Jolly-like inclusions (g, arrow head; Fig. 1). Eosinophils were unaffected, retaining their lobated morphology (h). A subsequent bone marrow examination demonstrated intermediate PPHA cells (i), but no other identifiable dysplasia or increase in the blasts. Conventional cytogenetics revealed a normal male karyotype (46, XY [20]) and engraftment analyses on the blood and marrow samples confirmed the donor origin of the myeloid elements (CD15 positive fraction). These ancillary studies excluded the possibility of relapsed or chemotherapy-related myeloid neoplasia. The neutrophils resumed their normal segmentation (j) 4 months later. Coincidentally, the clinical note stated that the tacrolimus dose was reduced to 0.5 mg per day from initial dose of 1.5 mg per day and prednisone was further tapered to 5 mg per day 7 weeks before the disappearance of pseudo-Pelger-Huët neutrophils in the routine peripheral blood smear examination. Therefore, the appearance of PPHA seemed to correlate with introduction of tacrolimus, and subsequent normalization of neutrophilic nuclear segmentation could be due to its dose reduction. Administration of multiple other medications confounds definitive delineation of the causative factors in this case.

Pelger-Huët anomaly (PHA) was first described by Karl Pelger in 1928 [1], and was documented by G. J. Huët in 1931 as a benign autosomal dominant anomaly affecting granulocytic segmentation [2]. This hereditary anomaly is characterized by granulocytes with abnormally condensed chromatin and hypolobated nuclear contours, which can be round, oval, peanut-shaped, coffee bean-shaped or symmetrically bilobed. Despite the morphologic abnormalities, the granulocytes are functional, thus individuals with hereditary PHA are not more susceptible to bacterial infections. Conversely, PPHA is an acquired neutrophilic

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Fig. 1 Reversible Pseudo-Pelger-Huët anomaly in a hematopoietic stem cell transplant recipient. Note the hypolobated neutrophils with abnormally clumped chromatin and varied nuclear shapes in peripheral blood (a–g), an eosinophil with normal segmentation in peripheral

blood (h), intermediate PPHA (i) with a normal appearing erythroid normoblast (i, inset) on the bone marrow touch imprint, and eventually normalized neutrophilic segmentations in peripheral blood (j)

anomaly with morphology resembling hereditary PHA. While its presence in some cases of myeloid neoplasms, namely MDS and AML with myelodysplasia, renders a diagnostic implication, PPHA can also be induced by many other etiologies [3]. One of the dominant etiologies for this morphologic deviation is the increased use of transplant medications due to increased allogeneic organ or bone marrow transplants in the recent years. This neutrophilic abnormality in allogeneic transplant recipients has been reported to be associated with the use of tacrolimus and/or mycophenolate mofetil [4, 5], and the effects may be synergistic with the concomitant use of other drugs [4, 6]. The change is apparently reversible since neutrophils resume their segmentation following dose reduction or discontinuation of transplant medications in the reported cases [4–6]. Because of the conventional opinion of PPHA as a marker for myelodysplasia [3], the presence of these iatrogenic PPHA in peripheral blood may cause diagnostic confusion, particularly in patients with bone marrow or hematopoietic stem cell transplant for MDS/AML. Recognition of its benign nature in these cases can avoid unnecessary diagnostic intervention and medical treatment. While the underlying mechanism of PPHA is currently unclear, recent identification of mutated lamin B receptor gene in hereditary Pelger-Huët anomaly [7] may shed light and lead to further investigation of acquired forms (PPHA),

including both medication-related and the ones associated with myelodysplastic neoplasm.

References

1. Pelger K. Demonstrate van een paar zeldzaam voorkomende typen van bloedlichaampjes en bespreking der patienten. *Ned Tijdschr Geneesk.* 1928;72:1178.
2. Huët GJ. Familiaire anomalie der leucocyten. *Ned Tijdschr Geneesk.* 1931;75:5956–9.
3. Cunningham JM, Patnaik MM, Hammerschmidt DE, Vercellotti GM. Historical perspective and clinical implications of the Pelger-Huët cell. *Am J Hematol.* 2009;84:116–9.
4. Etzell JE, Wang E. Acquired Pelger-Huët anomaly in association with concomitant tacrolimus and mycophenolate mofetil in a liver transplant patient: a case report and review of the literature. *Arch Pathol Lab Med.* 2006;130:93–6.
5. Asmis LM, Hadaya K, Majno P, Toso C, Triponez F, Starobinski M. Acquired and reversible Pelger-Huët anomaly of polymorphonuclear neutrophils in three transplant patients receiving mycophenolate mofetil therapy. *Am J Hematol.* 2003;73:244–8.
6. Kennedy GA, Kay TD, Johnson DW, et al. Neutrophil dysplasia characterised by a pseudo-Pelger-Huet anomaly occurring with the use of mycophenolate mofetil and ganciclovir following renal transplantation: a report of five cases. *Pathology.* 2002;34:263–6.
7. Hoffmann K, Dreger CK, Olins AL, et al. Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huët anomaly). *Nat Genet.* 2002;31:410–4.